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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,436	12/22/2004	Hilde Azjin	TIP0015 US	7541

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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,436	AZJIN ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2 and 5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed 20 November 2008. Claims 1, 3 and 4 have been cancelled. Claims 2 and 5 are pending and currently examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 2 and 5 under 35 U.S.C. §112, second paragraph, as being indefinite is withdrawn in response to the Applicants' amendment to the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 2 and 5 under 35 U.S.C. §103(a) as being obvious over Stein *et al.* (1994, hereinafter "Stein") in view of Servais *et al.* (10 March 2001, GenBank Accession Number CAB 86592, hereinafter "Servais") and Kim *et al.* (2001, hereinafter "Kim") is maintained.

The instant claims are directed to a method for evaluating the effectiveness of an HIV reverse transcriptase inhibitor (RTI) for a second anti-HIV therapy comprising:

(i) receiving a sample from an HIV-infected patient who has been treated with a first anti-HIV therapy;

(ii) determining whether said sample from said HIV-infected patient comprises a nucleic acid encoding HIV reverse transcriptase having at least one mutation at the position 194, wherein the wild type amino acid glutamate is mutated to glycine (E194G) as compared to the wild-type HIV strain IIIB/LAI;

(iii) introducing said HIV reverse transcriptase inhibitor for said second anti-HIV therapy to said sample from said HIV-infected patient containing said mutation;

(iv) comparing the effectiveness of said inhibitor in said samples containing said reverse transcriptase mutation with a sample containing no said mutation; and

(v) correlating the presence of said at least one mutation of step (ii) to a change in effectiveness of said HIV reverse transcriptase inhibitor.

Stein discloses receiving a sample from an HIV-infected patient and determining whether the sample comprises a nucleic acid encoding HIV reverse transcriptase having at least one mutation at position 194 from wild type amino acid glutamate (page 216, Table I); and correlating the presence of the mutation to a change in effectiveness or susceptibility of a nucleoside reverse transcriptase inhibitor (NRTI), azidothymidine (AZT) (page 117 and Table II).

Stein does not disclose the specific amino acid change from glutamate (E) to glycine (G) at position 194 (E194G) or evaluating the effectiveness of a HIV RTI for a pre-treated patient.

According to the sequence submitted to the GenBank under accession number CAB86592, Servais discloses the E194G mutation in the reverse transcriptase in samples from patients who have been treated with a first anti-HIV therapy containing zidovudine and zalcitabine.

Stein and Servais do not expressly suggest introducing a second therapy RTI to a pre-treated patient sample containing the drug-resistant mutation(s).

However, Kim discloses a method of introducing HIV nucleoside reverse transcriptase inhibitor, 3'-fluoro-3'-deoxythymidine (FLT), to both a wild-type HIV-1 isolate and multidrug-resistant HIV-1 patient isolates containing known mutations. The activity of FLT against the patient isolates are determined by drug susceptibility assays and compared to the activity against the wild-type isolate (Abstract). The FLT would be a second anti-HIV therapy if the patients have already been treated with a first therapy.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the drug-resistance mutation profiles taught by Stein and Servais because both evaluation methods use the same RTI, AZT, and to modify the evaluation method of Stein to further include the steps as suggested by Kim. One having ordinary skill in the art would have been motivated to do this so that the E194G mutation contributes to a more complete and accurate drug evaluation for any novel HIV RTIs while the *in vitro* test of introducing a RTI to a pre-treated patient sample containing the known RTI-resistant mutation(s), as a result of the first anti-HIV therapy, helps identify more potent RTIs in a rapid assay. Thus, the invention as a whole was

clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments have been fully considered but are not persuasive. Applicant argues that Stein does not disclose or suggest the use of reverse transcriptase mutation for evaluating any other HIV RTI or the use of HIV RTI for a second anti-HIV therapy. However, this argument mischaracterizes the rejection because Stein was offered for teaching the claim limitations of receiving a sample from an HIV-infected patient and determining the mutations, including the mutation of glutamate194, in the sample from said patient. Secondly, Servais discloses in a submitted GenBank sequence, as a result of similar approaches of sample collection and sequence analysis, that the HIV reverse transcriptase residue glutatmate 194 is mutated to glycine. Finally, Kim was offered for teaching evaluation of the effectiveness of a HIV RTI for a second anti-HIV therapy by testing *in vitro* in the sample from patient who has been treated with a first anti-HIV therapy. Therefore, these three references when viewed as a whole disclose all the claim limitations.

Applicant further argues that the data sheet of GenBank CAB86592 does not disclose or suggest the use of E194G mutation for evaluating HIV RTI or the use of HIV RTI for a second anti- HIV therapy. However, this step/limitation/component is taught by the combination of Stein and Kim. The obviousness of the combination does not hinge on whether Stein or Servais alone suggests using the E194G mutation for evaluating a HIV RTI in a second anti-HIV therapy. Rather, the motivation to combine

the Stein and Servais references was to use Stein's sequence analysis to detect mutations including at position 194, and more specifically, mutation to Glycine (E194G), as taught by Servais.

Applicant's arguments regarding the Servais publication cited in the GenBank CAB86592 sequence data are not germane to the rejection at issue because the Servais journal publication is not relied on for the rejection. Rather, the GenBank CAB86592 sequence submission is the reference to render obvious to one skilled in the art that the E194 mutation disclosed in Stein can be E194G.

Applicant also argues that Kim discloses effect of FLT or AZT on the PBMC cell line, not a sample from a patient, infected by HIV-1 isolates containing various mutations in reverse transcriptase. Examiner does not concur. The HIV-1 isolates containing various mutations in reverse transcriptase is collected from a sample of HIV-infected patient. Kim specifically discloses testing the antiviral activity of FLT on multi-drug-resistant HIV-1 patient isolates, which are cells infected by viral strains isolated from treated patients (abstract and page 402). Kim's disclosure expressly suggests evaluating the effectiveness of an HIV RTI (such as FLT) for a second anti-HIV therapy by introducing said HIV RTI to a sample of a patient viral strain containing multi-drug-resistant mutations.

Finally, Applicant argues that Kim does not disclose or suggest the E194G mutation, any use thereof, or the use of HIV RTI for a second anti-HIV therapy. The obviousness of the combination does not hinge on whether Kim alone suggests using the E194G mutation for evaluating a HIV RTI in a second anti-HIV therapy. Rather, the

motivation to combine the Stein, Servais and Kim references was to use Stein's sequence analysis to determine whether a sample from a patient who has been treated with a first anti-HIV therapy contains a mutation at residue 194 in the reverse transcriptase, which can be mutated to glycine as taught by Servais, and then to evaluate drug susceptibility of Stein's pre-treated patient HIV isolate to a second RTI using Kim's assay.

In response to Applicant's argument that there is no suggestion or motivation in any of the cited documents, the rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958, F2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); *In re Nilssen*, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); *Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning). In this case, the motivation or reason to combine Stein's mutation determination method with Kim's drug susceptibility assay, as set forth above,

is immediately apparent to one skilled in the art. Thus, a *prima facie* case of obviousness is properly established.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648

/Jeffrey S. Parkin/
Primary Examiner, Art Unit 1648

20 February 2009